clearly the invention as taught in the specification. Claim 26 has been amended to recite a method of treating a patient with diabetic nephropathy comprising administering to said patient in need of treatment from diabetic nephropathy, an amount of Sulodexide, or a pharmaceutically acceptable salt thereof, of at least 200 mg/day, said amount being sufficient to decrease albumin excretion rate without causing adverse side effects. Support for the amendment to claim 26 is found at page 6, line 31 to page 7, line 5 of the specification as originally filed. Claims 27 and 29 have been amended to correct typographical errors and/or recite the correct claim dependency. Claim 29 has also been amended that the Sulodexide or salt thereof is administered is administered in a single or divided dose from one to four times per day. Support for this amendment to claim 29 is found in the specification at page 10, line 16.

Claims 30-36 have been added. Support for new claim 30 is found in the specification at page 9, lines 27-29. Support for the newly added claims 31-36 is found in the specification as originally filed on page 7, lines 1-5.

No new matter is added by the amendments made herein.

Objections To The Claims

Claims 1 and 8-24 and claims 28-29 are objected to because of informalities noted by the Examiner. In response, Applicants have amended the claims such that the objections to the claims have been obviated.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 27 is rejected under 35 U.S.C. § 112, second paragraph, allegedly, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the recitation of "method of claim 15" lacks antecedent basis. In response, Applicants have amended claim 27 to recite "method of claim 26". In view of the amendment to claim 27, it is submitted that this rejection under Section 112, first paragraph, has been obviated and should be withdrawn.

Rejections under 35 U.S.C. § 102(b)

A. Claims 1-10 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,252,339 to Cristofori et al. ("Cristofori"). Applicants do not agree with the

Examiner's rejection and in no way acquiesce to this rejection or to the basis on which it is made. However, claims 1-25 have been canceled without prejudice in order to expedite issuance of claims to certain embodiments of the invention in the present application. Applicants fully reserve all rights to the subject matter of claims 1-25 and intend to pursue such subject matter is a related application. In addition, Applicants fully reserve all rights to respond to this rejection should it be raised in any subsequent application. Thus, in view of the cancellation without prejudice of claims 1-25, this Section 102(b) rejection has been obviated and Applicants respectfully request its removal.

B. Claims 26-27 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,496,807 to Marchi et al. ("Marchi"). According to the Examiner, Marchi discloses pharmaceutical compositions of sulodexide at a dosage of 500 to 1500 LRU for the treatment of diabetic nephropathy.

Applicants respectfully disagree with the Examiner. Marchi teaches dosages of 500 to 1500 LRU sulodexide per day to treat diabetic nephropathy, which is equivalent to 50 to 150 mg per day. However, Marchi does not teach a method for treating diabetic nephropathy by administering more than 150 mg sulodexide per day. In fact, Marchi only administered two capsules containing 250 LRU (25 mg) twice a day (column 3, lines 10-16 and column 4, lines 24-26 of Marchi); and (b) an injection of 600 LRU (60 mg) once a day (column 3, lines 35-40).

In contrast, the currently pending claims, as amended, are directed to a method of orally administering a pharmaceutical composition comprising an amount of sulodexide, or a pharmaceutically acceptable salt thereof, of at least 200 mg/day. As explained above, in order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Since Marchi does not teach each and every element of the claimed invention, Marchi cannot, and in fact does not, anticipate the claimed invention.

In view of the foregoing, Applicants respectfully submit that this Section 102 rejection is in error and must be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1-27 are rejected under 35 U.S.C. § 103(a), allegedly, as obvious over U.S. Patent No. 5,252,339 to Cristofori et al. ("Cristofori"), U.S. Patent No. 5,496,807 to

Marchi ("Marchi") and U.S. Patent No. 5,686,432 to Baggio et al. ("Baggio"). According to the Examiner:

> It would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of Cristofori, Baggio, and Marchi to arrive at the instant invention. One or ordinary skill would [be] aware of methods to increase the concentration of an active agent in order to obtain a desired effect. It would have been obvious to use the invention of Cristofori for the treatment of diabetic nephropathy since Marchi teaches compositions of sulodexide for the same purpose. Marchi also teaches the incorporation of the sulodexide compositions into controlled-release formulations. One would have been motivated to do so in order to provide effective treatment since factors such as the extent of the illness and body weight of the patient could render conventional compositions ineffective. Thus, the instant invention is seen to be within the purview of the skilled artisan.

Applicants respectfully disagree and submit that none of the cited references, either alone or in combination, renders obvious the claimed invention. Applicants note that claims 1-25 have been canceled without prejudice in order to expedite issuance of claims to certain embodiments of the invention in the present application. Applicants fully reserve all rights to the subject matter of claims 1-25 and intend to pursue such subject matter is a related application. In addition, Applicants fully reserve all rights to respond to this rejection should it be raised in any subsequent application with regard to the subject matter of claims 1-25.

Baggio teaches the administration of sulodexide by injection for treatment of renal insufficiency. Baggio does not teach, much less suggest, the oral administration of sulodexide. As discussed above, Marchi teaches dosages of 500 to 1500 LRU sulodexide per day to treat diabetic nephropathy, which is equivalent to 50 to 150 mg per day. However, Marchi does not teach a pharmaceutical composition comprising a unit dosage of sulodexide of 100 mg or more. Also as discussed above, Cristofori teaches a pharmaceutical composition of 25 to 500 mg of glycosaminoglycans, including but not limited to sulodexide, in the form of a gastro-resistant coated formulation. Cristofori does not teach or suggest the administration of sulodexide for the treatment of diabetic nephropathy.

Applicants submit that none of the references, alone or in combination, suggest the claimed methods for administering sulodexide in an amount of at least 200 mg per day to treat diabetic nephropathy. None of the references provide the motivation to increase the amount of sulodexide in the unit dosage to be administered for the treatment of diabetic nephropathy from that disclosed in the art.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). None of the cited references provide the required suggestion or expectation.

Moreover, the prior art, as discussed on page 4, line 25 to page 5, line 13 of the specification, actually taught away from the claimed higher dosages of sulodexide from that previously administered in view of the possible risks and side effects of administration of sulodexide. The specification teaches at page 4, lines 23-30:

> In addition, another reason for the use of such low doses was the concern over possible risks and side effects of a drug such as Sulodexide. For example Sulodexide is known to have antithrombotic activity equal to that of heparin, Thomas D.P. et al. Ann. N.Y. Acad. Sci., 556, 313 (1989) and to completely prevent clot formation at high doses. In primates the oral administration of 10 mg/kg of Sulodexide increased tissue plasminogen activator (TPA) from 5 to 10 ng/ml and produced an increase of U-PA from 3 to 6.5 ng/ml. This suggests that Sulodexide is a strong anticoagulant, antithrombotic and profibromolytic agent. Callas D.D. et al., Thromb. Hemost., 19 (Suppl. 1), 49 (1993).

Further, and most importantly, the administration of sulodexide at the claimed higher dosages provided unexpected results compared to treatment with lower dosages. The Examiner's attention is invited to page 8, lines 17-32 and to Table 1 on page 9 of the specification. As set forth in Table 1, administration of 200 mg per day of sulodexide resulted in a statistically significant improvement in treatment as compared to administration of 100 mg per day. Moreover, this effect was even observed in those patients already taking ACE inhibitors, which may be of particular import to NIDDM or DM2 nephropathic patients who respond less well to ACE inhibitors and who comprise the fastest growing group of patients with end stage renal disease. Additionally, this statistically significant effect surprisingly persisted up to 4 months after cessation of treatment, which may permit some patients to take sulodexide on an intermittent basis.

Additionally, as taught in the specification, no side effects were observed in that there was no significant change in hemotologic, coagulation and liver function parameters. Moreover, no plateau effects were seen, which was surprising and unexpected since the dose used in the study described in the specification was twice the maximum dose used in prior studies. Applicants respectfully remind the Examiner that secondary considerations such as unexpected results must be taken into account in determining the obviousness or nonobviousness of the invention. See *e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

In view of the foregoing, and in particular in view of the unexpected results, Applicants submit that the rejection under Section 103 is in error and respectfully request its withdrawal.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the present application. Claims 26, 27 and 29-36 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicants request that the Examiner call Geraldine F. Baldwin at (212) 790-2296 if any questions or issues remain.

Respectfully submitted,

by William T. Ellis
REG NO. 40,203

Date September 24, 2002

Geraldine F. Baldwin 31,232
Geraldine F. Baldwin (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

RECEIVED
SEP 2 6 2002
TECH CENTER 1600/2900

OIPE JC100
SEP 2 6 2002
PATENT & TRADEMARK OFFICE

EXHIBIT A

Serial No.: 09/873,234
Filed: June 4, 2001
Attorney Docket No.: 9457-023

MARKED-UP VERSION OF CLAIMS
UNDERLINED TEXT IS ADDED AND [BRACKETED TEXT] IS DELETED

26 (once amended). A method of treating a patient with diabetic nephropathy comprising orally administering to [a human] said patient in need of treatment from diabetic nephropathy, an amount of Sulodexide, or a pharmaceutically acceptable salt thereof, of at least [100] 200 mg/day,[up to 1000mg/day,] said amount being sufficient to decrease albumin excretion rate without causing adverse side effects.

27 (once amended). The method of claim [15] 26 wherein Sulodexide or salt thereof is administered orally as a tablet, a capsule or a liquid suspension.

29 (once amended). The method of claim [15, 16 or 17] 26 wherein the Sulodexide or salt thereof is administered in a single or divided dose from [in] one to four [unit doses] times per day.